Amphiphilic Urethane Acrylate Hydrogels: pH Sensitivity and Drug-Releasing Behaviors

DOO-HYUN LEE, JIN-WOONG KIM, KYUNG-DO SUH

Division of Chemical Engineering, College of Engineering, Hanyang University, Seoul 133-791, Korea

Received 14 March 1998; accepted 5 September 1998

ABSTRACT: Amphiphilic urethane acrylate hydrogels containing ionic groups (dimethylolpropionic acid, DMPA) were prepared with varying the molecular weight of the hydrophobic segment (polyether type, PTMG), and their swelling and drug-releasing behaviors were examined. Amphiphilic property for the hydrogels could be confirmed by observing the swelling in both water and organic solvent (benzene) readily. High pH sensitivity was observed due to the carboxylic groups incorporated into the molecular backbone of the urethane acrylate molecules. Owing to the amphiphilic property, it was possible to load hydrophilic (riboflavin selected) and hydrophobic (indomethacin selected) drugs in the network with ease. Each drug successfully released from the network of the urethane acrylate. The releasing behaviors were dependent upon the swelling ones and followed Fickian diffusion. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 72: 1305–1311, 1999

Key words: amphiphilic urethane acrylate hydrogels; ionic groups; hydrophobic segment; pH sensitivity; releasing behaviors; Fickian diffusion

INTRODUCTION

Amphiphilic networks are random assemblages of hydrophilic and hydrophobic chains linked to three-dimensional crosslinked systems.[1–6] Because these networks swell in water as well as in an organic nonpolar solvent, they may be regarded as a special class of hydrogels. These hydrogels are extensively used in many biomedical applications, for example, implants[7–9] and drug delivery devices.[10,11] However, in conventional hydrogels, the amphiphilicity has also been commonly observed, even though there is some difference in the degree of hydrophilicity and/or hydrophobicity of the gel network. This is because every hydrogel network simultaneous has both hydrophilic and hydrophobic components. Therefore, a newly designed hydrogel network that has a distinctive domain structure was required for a selective application relative to the amphiphilicity of the network.

In our previous works,[12] we have studied the preparation of amphiphilic urethane acrylate hydrogels containing ionic groups as a hydrophilic domain and polyether soft segments as a hydrophobic domain in the same network. This peculiar network structure was achieved by the synthesis of a water-soluble urethane acrylate anionomer by a stepwise reaction procedure.[12–14] Consequently, this urethane acrylate anionomer synthesized had an ability to crosslink by the vinyl groups on both ends, as well as to hydrate sufficient water by the carboxylated groups in its molecular backbone. Especially, when hydrogel was prepared, the heterophasic gel structure was observed by the phase separation of ionic groups from the hydrophobic urethane acrylate network. Owing to this heterophasic gel structure, the net-

Correspondence to: K.-D. Suh.

Contract grant sponsor: Korean Science and Engineering Foundation; contract grant number: 96-0300-12-01-3.

Journal of Applied Polymer Science, Vol. 72, 1305–1311 (1999)
 CCC 0021-8995/99/101305-07

Table I The Composition for the Synthesis of Urethane Acrylate Ionomers[a]

			PTMG[b]					
Symbol	IPDI	DMPA	1.0×10^3	1.4×10^3	2.0×10^3	HEMA	TEA[c]	DMPA (wt %)
ID1	20	6.03	22.49	—	—	5.85	4.54	10.23
ID2	20	6.03	—	31.49	—	5.85	4.54	8.88
ID3	20	6.03	—	—	44.98	5.85	4.54	7.41

[a] All units are in grams.
[b] Molecular weight of polytetramethylene glycol (PTMG).
[c] Triethylamine (TEA) was used as a neutralization agent.

work absorbed a large amount of water in the course of swelling, compared it with general amphiphilic hydrogles. In addition, high mechanical properties were observed in the wet state, which were attributed to the inherently strong network structure of the urethane acrylate.

In this study, as a subsequent work for these amphiphilic hydrogels, pH sensitivity was observed. The ionic group incorporated (carboxylic group) was expected to show a good reversible contraction and expansion with pH of the medium.[15–17] Drug-releasing behaviors were also examined. Finally, swelling and drug-releasing behaviors were studied with the molecular weight of soft segment (PTMG), pH, and kind of drug.

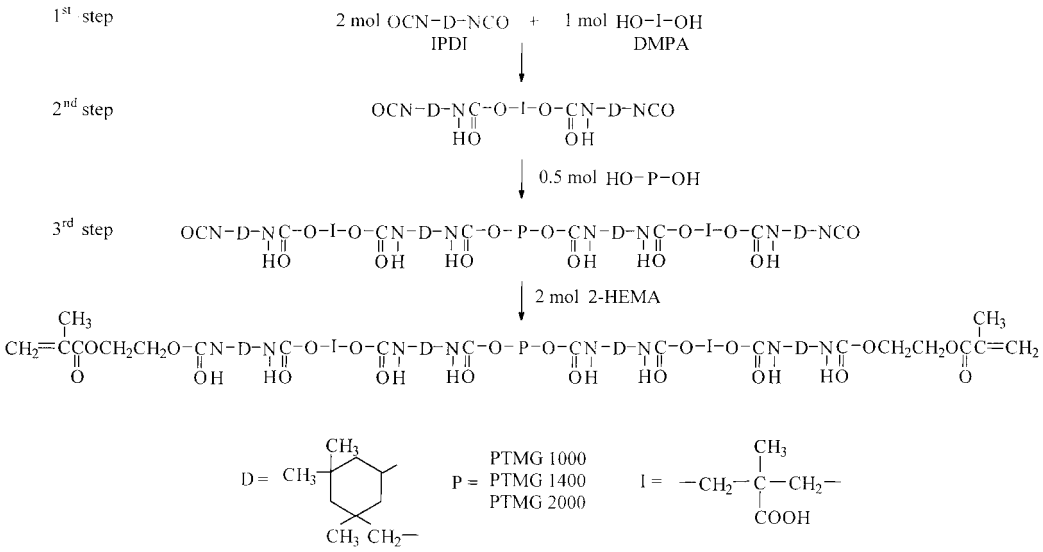
EXPERIMENTAL

Materials

Isophorone diisocyanate (IPDI, Junsei Chemical Co.) was vacuum distilled before use. Polytetramethylene glycol (PTMG, 1.0×10^3, 1.4×10^3, and 2.0×10^3 g(mol^{-1}, Hyosung BASF), dimethylolpropionic acid (DMPA, Aldrich Chemical Co.), Ammonium persulfate (AMPS, Yakuri Pure Chemicals Co.), and 2-hydroxyethyl methacrylate (HEMA, Aldrich Chemical Co.) were used as received. The drugs, riboflavin (Junsei Chemical Co.) and indomethacin (Sigma Chemical Co.), were used as a crystalline powder, purity 99.7%.

Synthesis of Urethane Acrylate Ionomers[9,12–14]

The composition for the synthesis of urethane acrylate ionomers is listed in Table I. The reaction procedure and molecular structure designed are presented in Scheme 1. Here, ID is the IPDI-based urethane acrylate ionomer. In the ID series, serial numbers 1, 2, and 3 correspond to the molecular weight of PTMG, 1.0×10^3, 1.4×10^3, and 2.0×10^3 g · mol^{-1}. All reactions were carried out in the four-necked glass reactor equipped with a stirrer, a reflux condenser, thermocouples,



Scheme 1 The reaction procedure and molecular structure of the urethane acrylate ionomers.

and nitrogen gas inlet system. In the first step, diisocyanate was poured into the glass reactor, and nitrogen gas was let in for 10 min to eliminate the residual moisture. After dissolving 1 wt % of dibutyltindilaurate, DMPA dissolved in DMAc was dropped into the reactor slowly at room temperature. The reaction was carried out at 80°C for 4 h so that 2 mol of IPDI reacted with the 1 mol of DMPA, resulting in the molecular structure having a carboxylic acid group in the middle and isocyanates on the ends. The change of NCO value during reaction was determined using dibutylamine back titration method to find out the end point of reaction.[18]

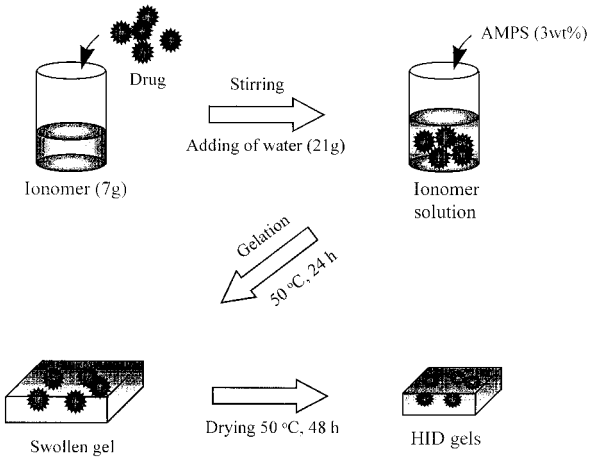
In the second step, 0.5 mol of PTMG was added slowly into the reactor to incorporate a soft segment into the molecular backbone with the same method as the first step. In the last step, after dissolving 1 wt % dibutyltindilaurate into the reactor, 2 mol of HEMA was reacted to the residual NCO group at 45°C for 12 h, which introduce reactive vinyl group in the molecular ends. The reaction end point was determined by the disappearance of an NCO stretching peak (2270 cm^{-1}) through IR spectroscopy.

To purify DMAc, unreacted HEMA, and DMPA, the reaction mixture was precipitated from the water and filtered several times. The crude product was dried *in vacuo.* Carboxylic acid groups were ionized with the appropriate amount of triethylamine at room temperature for 1 h.

Preparation of Urethane Acrylate Hydrogels

The mixture of ionomer (7 g) and deionized distilled (DDI) water (21 g) including AMPS (3 wt %, based on total ionomer weight) was transferred into a mold (100 × 150 × 2 mm) to carry out the gelation. Then, the gelation performed at 50°C for 24 h. After the gelation was complet, all samples were fully washed with a large amount of DDI water and methanol and dried *in vacuo*. Here, we used HID for gels prepared with IDs.

For the preparation of the hydrogels containing the drug, riboflavin (7.5, 16, and 24 mg) or indomethacin (24 mg) was first dissolved in the ionomer. Then, gelation was carried out with the same procedure mentioned above. The hydrogels obtained were optically transparent, showing the complete solubility of the drug in the matrix. Hydrogels prepared were cut into discs (0.7 g), where the diameter is 0.9 ± 0.2 mm and thickness of 1 ± 0.2 mm for the measurement of the swelling ratio and drug release. In Scheme 2, the precise procedure for the preparation of drug-loaded hydrogels is represented.



Scheme 2 The schematic procedure for the preparation of drug-loaded hydrogels.

Measurements

Molecular weight distributions were measured by a model 410 GPC, equipped with Styragel HR 1–4 columns from Waters Associates at 25°C. The flow rate of the carrier solvent, THF, was 0.5 mL/min. The average molecular weights calculated on the basis of the molecular weight vs. retention volume curve of monodisperse polystyrene standards were $M_n = 5.4 \times 10^3 \sim 7.1 \times 10^3\ g \cdot mol^{-1}$ and $M_w = 8.3 \times 10^3 \sim 1.4 \times 10^4\ g \cdot mol^{-1}$.

The swelling experiments were carried out in benzene or buffer solutions (pH 4, 7.4, and 9) at room temperature. The ionic strength of the buffer solutions was fixed with 0.1 in all cases. Swelling ratio was determined using the conventional gravimetric method as follows:

$$\text{Swelling Ratio} = \frac{W_s - W_d}{W_d},$$

where W_s is the weight of the sample swollen by solvent, and W_d the weight of the dried sample.

Drug-loaded hydrogel samples were placed in a 50-mL buffer solutions (pH 4, 7.4, and 9) at 37°C under a mild stirred condition. Then, the release of the drug in the medium was determined by taking out an aliquot (3 mL) at the same time intervals and measuring its absorbance at the λ_{max} (riboflavin: 437 nm, and indomethacin: 318 nm) of the drug using a Shimadzu UV spectrophotometer (UV-2101PC). The amount of the re-

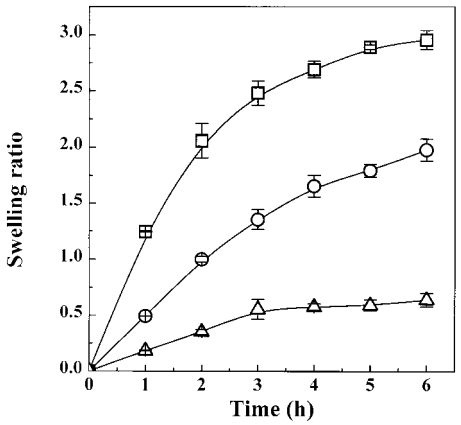


Figure 1 The swelling ratios of HID1 gel (□), HID2 gel (○), and HID3 gel (△) as a function of time in pH 7.4 at 25°C.

leased drug was computed by comparing the absorbance with the standard curve prepared.

RESULTS AND DISCUSSION

Urethane acrylate ionomer has been designed with peculiar molecular structure, as shown in Scheme 1. It has two vinyl groups enable to crosslink each other at both ends, and two ionic groups (carboxylate ions) to hydrate in the molecular backbone. In addition, it also has a long polyether soft segment showing hydrophobicity in the middle of the molecule. Therefore, hydrogel prepared with this urethane acrylate ionomer can be expected to show an amphiphilic property due to hydrophilic ionic groups and hydrophobic polyether soft segments in the network. Moreover, the hydrophilic and hydrophobic drugs can be loaded in the hydrogels due to the amphiphilic properties.

Amphiphilic Property of Urethane Acrylate Hydrogels

Figures 1 and 2 show the swelling ratios of urethane acrylate hydrogels (HID) as a function of time in pH 7.4 buffer solution and benzene, respectively. Equilibrium swelling ratios were reached in the order of 6 h for all samples. The degree of swelling ratio changed with the network composition.

As the data indicates, HID gels swelled in both solvents, which shows they have amphiphilic property. However, for HID gels of a low molecular weight of the soft segment, the degree of swelling was dominated by hydrophilic property. This result was assumed to be due to the higher charge density of the gel network. The HID gel of the lower molecular weight of the soft segment has a relatively smaller phase volume of the hydrophobic soft segment (ID1, ID2, and ID3 resins contain 10.24, 8.88, and 7.41 wt % of DMPA, respectively). For HID gels of high molecular weight of the soft segment, the degree of swelling was dominated by the hydrophobic property. Under a similar assumption mentioned above, this result can also be explained by a lower charge density of gel network and a higher phase volume of the hydrophobic soft segment.

pH Sensitivity of Urethane Acrylate Hydrogels

Figure 3 shows the swelling and deswelling dynamics of HID gels by cycling between pH 4 and 9 at room temperature. It appeared that swelling and deswelling of HID gels were significantly reversible. As the molecular weight of the soft segment reduced, high pH sensitivity could be obtained. This was resulted from the high content of —COOH groups in the gel network.

Their contraction and expansion were due to changes in ionization.[3, 19, 20] During the swelling cycle at pH 9, the residual —COOH groups are initially in their form and ionized upon immersing in an aqueous base. In addition to the electrostatic repulsion between the ionized groups, osmotic pressure caused by the presence of the mobile counterions also increased swelling. On the contrary, during deswelling upon immersing in

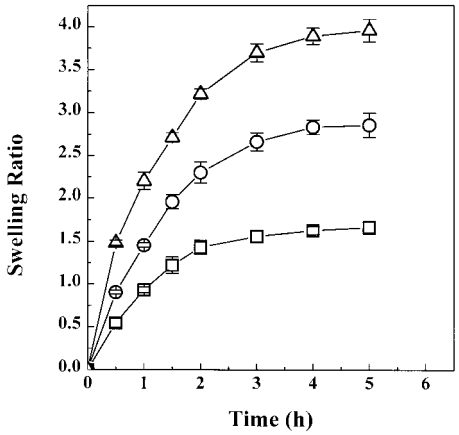


Figure 2 The swelling ratios of HID1 gel (□), HID2 gel (○), and HID3 gel (△) as a function of time in benzene at 25°C.

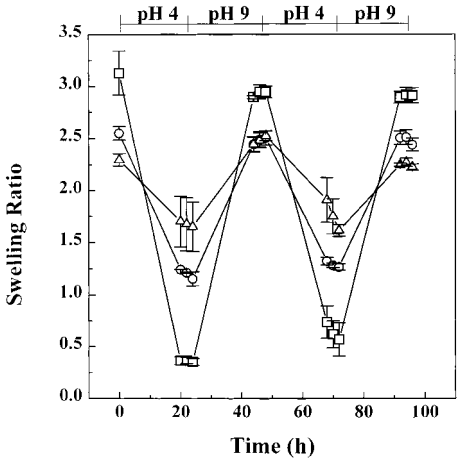


Figure 3 Equilibrium swelling ratios of HID1 gel (□), HID2 gel (○), and HID3 gel (△) as a function of time after repeated changes of pH between pH 4 and pH 9 at 37°C.

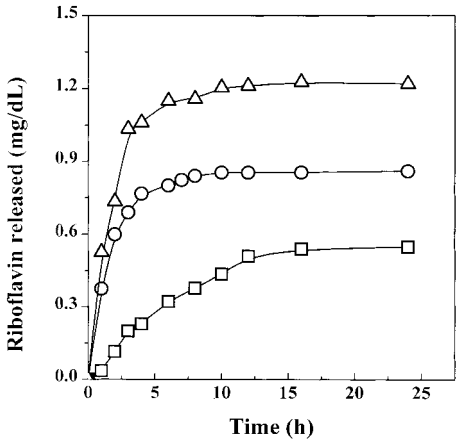


Figure 4 Riboflavin released from HID gels as a function of time for different loaded amounts of riboflavin; 0.75 mg (□), 1.6 mg (○), and 2.4 mg (△), in pH 7.4 at 37°C. The dimensions of the HID gel discs was 0.9 ± 0.2 mm diameter and 1 ± 0.2 mm thickness.

aqueous acid at pH 4, the ionization of the carboxylated groups is suppressed and the nonionic form becomes dominating. Consequently, the shielding of the ionized groups by the H^+ groups resulted in contraction—that is, deswelling.[16]

Drug-Releasing Behaviors

The synthesis of the drug-loaded hydrogels by the method shown in Scheme 2 has the following advantages; the releasing time of the drug from the hydrogels increases, which means an improvement in the control of the drug delivery. This fact can be a consequence of a better distribution of the drug in the polymer matrix; the amount of the drug included in the gel can be known from the beginning of the gel synthesis, and the maximum amount of drug included is higher than the one included by immersion.[21,22]

In our study, the direct drug incorporation into the feed mixture was successful. This was possible by the hydrophobic long tetramethylene oxide groups in the network, showing a good solubility for the drugs.

Figure 4 shows the amounts of riboflavin released from HID1 gels as a function of time for the different loaded amount of riboflavin (0.75, 1.6, and 2.4 mg). The results obtained showed a good agreement with the literature;[21] the releasing amount of the drug was dependent on the initial amount of riboflavin in the feed mixture. Thus, the amount of riboflavin released was ordered as follows: $HID_{2.4} > HID_{1.6} > HID_{0.75}$.

Figure 5 shows the riboflavin releasing curves as a function of time for the HID gels having different molecular weights of the soft segment (PTMG) in pH 7.4 buffer solution. The degree of riboflavin released was enhanced as the molecular weight of the soft segment decreased. The releasing behaviors were almost consistent with the swelling behaviors of Figure 1. Generally, drug release from the network is swelling controlled—that is, the out-diffusion rate is a function of the extent of hydration.[23,24] Therefore, in this system, the result suggests that the drug-

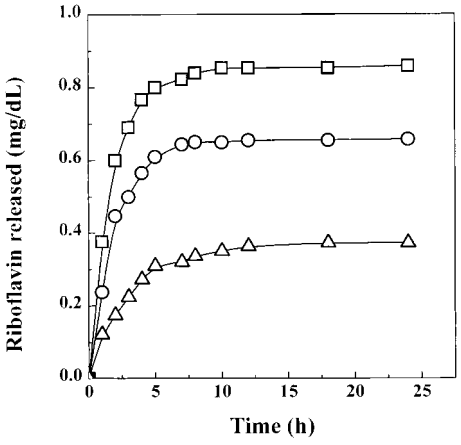


Figure 5 Riboflavin released from HID1 gel (□), HID2 gel (○), and HID3 gel (△) as a function of time in pH 7.4 at 37°C. The dimension of the HID gel discs was 0.9 ± 0.2 mm diameter and 1 ± 0.2 mm thickness

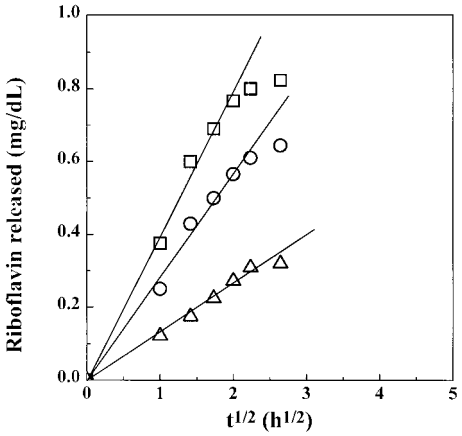


Figure 6 Riboflavin released from HID1 gel (□), HID2 gel (○), and HID3 gel (△) as a function of (time)$^{1/2}$ in pH 7.4 at 37°C.

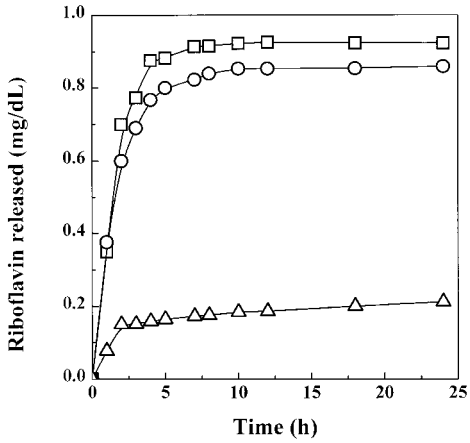


Figure 8 Riboflavin released from HID1 gels as a function of time with varying pH; pH 9 (□), pH 7.4 (○), and pH 4 (△), at 37°C. The dimension of the HID gel discs was 0.9 ± 0.2 mm diameter and 1 ± 0.2 mm thickness.

releasing behaviors was controlled by the swelling behaviors.

To confirm the Fickian diffusion, the riboflavin-releasing curves of Figure 5 were replotted against the square root of time and shown in Figure 6. HID gels showed the release by close to the Fickian diffusion. This was believed to be attributed to the high hydrophilicity of these gels, which would lead one to expect fast relaxation of the gel network (i.e., diffusion control by penetration diffusion) and Fickian kinetics.[1]

Figure 7 shows the indomethacin-releasing curves as a function of time for the HID gels having different molecular weights of the soft segment (PTMG) in pH 7.4 buffer solution. Peculiarly, in this study, it was observed that the indomethacin, a hydrophobic drug, could be loaded in the HID gels with ease. This was possibly interpreted by the amphiphilic property of the network. The indomethacin was also released successfully from the HID gels, even though it was hydrophobic drug. The releasing curves were dependent on the swelling behaviors of Figure 1.

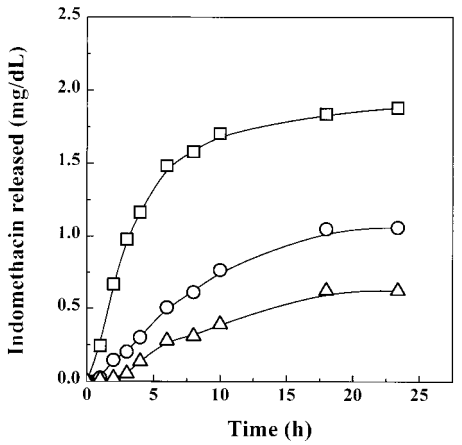


Figure 7 Indomethacin released from HID1 gel (□), HID2 gel (○), and HID3 gel (△) as a function of time in pH 7.4 at 37°C. The dimension of the HID gel discs was 0.9 ± 0.2 mm diameter and 1 ± 0.2 mm thickness.

Figure 8 shows the riboflavin-releasing curves as a function of time for the HID1 gel with pH. As shown, the degree of riboflavin-releasing was enhanced as the pH of the medium increased. This was because the ionization of ionic groups (—COOH groups) increased at high pH. However, at low pH, because of the shielding of the ionic groups, the swelling of the gel network was restricted, resulting in a lower degree of the riboflavin release.

CONCLUSION

Amphiphilic urethane acrylate hydrogels containing ionic groups showed amphiphilic property due to hydrophilic ionic groups and hydrophobic polyethers comprising the urethane acrylate network. Especially, the molecular weight of the hydrophobic segments had an effect on the swelling ratio, because of its hydrophobic interaction. In particular, because of the ionic groups in the hydrogels, pH-dependent swelling behaviors were observed. In the drug-releasing study it was found that

hydrophilic and hydrophobic drugs could be loaded successfully, mainly due to the amphiphilic property, and drug-releasing behaviors were controlled by the swelling behaviors.

This work was supported by Korean Science and Engineering Foundation (96-0300-12-01-3). D.-H. Lee and J.-W. Kim are grateful to the Graduate School of Advanced Materials and Chemical Engineering at the Hanyang University for a fellowship.

REFERENCES

1. Keszler, B.; Kennedy, J. P.; Mackey, P. W. J Controlled Release 1993, 25, 115.
2. Lan, N.; Corneillie, S.; Schacht, E.; Davies, M.; Shard, A. Biomaterials 1996, 17, 2273.
3. Keszler, B.; Kennedy, J. P. J Polym Sci Polym Chem 1995, 32, 3153.
4. Ivan, B.; Kennedy, J. P.; Mackey, P. W. Polymeric drugs and drug delivery system; American Chemical Society: Washington, DC, 1991.
5. Kim, J. Y.; Suh, K. D. Colloid Polym Sci 1996, 274, 1025.
6. Kim, J. Y.; Suh, K. D. Polym Bull 1996, 38, 403.
7. Chen, D.; Kennedy, J. P.; Allen, A. J.; Kory, M. M.; Ely, D. L. J Biomed Mater Res 1989, 23, 1327.
8. Weber, M.; Standler, R. Polymer 1989, 29, 1071.
9. Chen, D.; Kennedy, J. P.; Allen, A. J. J Macromol Sci Chem 1988, A25, 389.
10. Agurwal, S.; Sumana, G.; Gupta, D. C. J Appl Polym Sci 1997, 28, 1299.
11. Seymour, L. W.; Duncan, R.; Duffy, J.; Ng, S. Y.; Heller, J. J Controlled Release 1994, 31, 201.
12. Kim, J. W.; Suh, K. D. Colloid Polym Sci 1998, 276, 342.
13. Kim, J. W.; Suh, K. D. J Macromol Sci Pure Appl Chem 1998, A35(9), 1587.
14. Kim, J. W.; Suh, K. D. J Appl Polym Sci, 1998, 69, 1079.
15. Park, T. G.; Hoffman, A. S. J Appl Polym Sci 1992, 46, 659.
16. Harland, R. S.; Prud'homme, R. K. Polyelectrolyte Gels; American Chemical Society: Washington, DC, 1992.
17. Peppas, L. B.; Peppas, N. A. Chem Eng Sci 1991, 46, 715.
18. David, D. J.; Staley, H. B. Analytical Chemistry of Polyurethane, High Polymer Series, XVI, Part III; Wiley-Interscience: New York, 1969.
19. Vazquez, B.; Gurruchaga, M.; Gonl, I.; San Roman, J. Biomaterials 1997, 18, 521.
20. Peppas, L. P.; Peppas, N. A. J Controlled Release 1989, 8, 267.
21. Teijon, J. M.; Trigo, R. M.; Garcia, O.; Blanco, M. D. Biomaterials 1997, 18, 383.
22. Trigo, R. M.; Blanco, M. D.; Teijon, J. M.; Sastre, R. Biomaterials 1994, 15, 1181.
23. Yasuda, H.; Lamaze, C. E.; Ikenberry, L. D. Makromol Chem 1968, 118, 19.
24. Korsmeyer, R. W.; Peppas, N. A. J Controlled Release 1984, 1, 89.